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(54) Title: REDUCTION OF HAIR GROWTH EMPLOYING SULFHYDRYL REACTIVE COMPOUNDS			
(57) Abstract  A method of reducing the rate of mammalian hair growth includes topically applying a composition containing a sulfhydryl reactive compound to the skin.			

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**"REDUCTION OF HAIR  
GROWTH EMPLOYING SULFHYDRYL REACTIVE COMPOUNDS"**

Reduction of Hair Growth

The invention relates to reducing hair growth in mammals.

Hair proteins include a fairly large  
5 quantity of the amino acid cysteine, which includes a thiol (-SH) group. It is the formation of disulfide bonds between cysteine residues in the hair proteins, to form cystine, that give hair its strength and character.

10 It is known in the art to use depilatory compositions to remove hair from, e.g., legs. Such compositions, when applied to the skin, digest the hair, in part, by breaking down the disulfide bonds in the hair. Such  
15 compositions typically include a chemical agent like calcium thioglycolate that aids the digestion process.

We have discovered that the rate of mammalian (including human) hair growth can be  
20 reduced by applying a non-depilatory composition including sulfhydryl active compounds to the skin. Sulfhydryl active compounds, as used herein, are compounds that include a free -SH group, thiols without a free -SH group, and  
25 thiols or disulfides that can be converted to a molecule with a free -SH group in cells. Non-depilatory, as used herein, is a composition

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which after a single topical application does not result in hair removal and/or degradation.

Without being bound to any theory, it is believed that sulfhydryl active compounds  
5 reduce hair growth at least in part by one or more of the following mechanisms. During hair growth, cysteine is incorporated into protein chains. The -SH groups of cysteine residues in the protein chains form disulfide bonds (and  
10 cystine), binding the protein chains together as part of the normal hair growth. Sulfhydryl active compounds, applied topically, penetrate the hair follicle and interfere with hair growth by (1) reacting with free cysteine to form a  
15 mixed cysteine-sulfhydryl active compound disulfide bond, resulting in there being less cysteine available for incorporation into disulfide bonds present in hair proteins; (2) reducing the disulfide bond in cystine in the  
20 hair proteins, at the same time forming a mixed cysteine-sulfhydryl active compound disulfide bond; and (3) reducing the disulfide bond in cystine, without concomitant formation of the mixed disulfide bond.

25 Preferred sulfhydryl active compounds with a free -SH group include thiosalicylic acid, D-cysteine, 2-mercaptoethylamine (cysteamine), captopril, N-acetyl-L-cysteine, cysteinylglycine, 2,3-dimercapto-1-  
30 propanesulfonic acid, meso-2,3-dimercaptosuccinic acid, dimethylcysteamine, diethyldithiocarbamic acid, D-penicillamine, L-cysteine methyl ester, and L-cysteine ethyl ester.

35 Preferred sulfhydryl active compounds without a free -SH group include 3,3'-thiodipropionic acid, isethionic acid, 3-

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carboxypropyl disulfide, 3,3'-thiodipropionic acid dilauryl ester, sulfasalazine, 3-(methylthio)-propylamine, 5'-deoxy-5'-methylthioadenosine, allyl sulfide, DL- $\alpha$ -lipoic acid (reduced form), and DL-methionine-S-methylsulfonium chloride.

Preferred sulfhydryl active compounds that are converted to free thiols in cells include phosphocysteamine, which is dephosphorylated to cysteamine in cells; penicillamine disulfide, which is reduced to free penicillamine in cells; and S-2-aminoethyl-L-cysteine, which is hydrolyzed to cysteamine and serine (inactive) in cells.

The sulfhydryl active compounds should not be of too high a molecular weight (greater than about 1000 daltons), or contain highly charged phosphate groups, or compounds that may not adequately penetrate the skin.

The composition contains, in addition to the sulfhydryl active compound, a non-toxic dermatologically acceptable vehicle or carrier which is adapted to be spread on the skin. The concentration of the compound may be varied over a wide range up to a saturated solution, preferably from 1% to 20% by weight. The reduction of hair growth increases as the amount of sulfhydryl active compound applied increases per unit area of skin; the maximum amount that can be effectively applied is limited primarily only by the rate at which the compound penetrates the skin. Generally, the effective amounts range from 100 to 2000 micrograms or more per square centimeter of skin.

The following specific examples are intended to illustrate more clearly the nature

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of the present invention without acting as a limitation upon its scope.

The inhibition in hair growth provided by compositions including the sulfhydryl active compounds was determined by following the Golden Syrian Hamster protocol, which is described in Shander et al., U.S. Pat. No. 5,132,293, Ahluwalia, U.S. Pat. No. 5,095,007 and Ahluwalia et al., U.S. Pat. No. 5,096,911. Four groups (eight animals in each group) of male intact Golden Syrian hamsters were provided. These animals were considered acceptable models for human beard hair growth in that they display oval shaped flank organs, one on each side, each about 8 mm. in major diameter, which grow thick black and coarse hair similar to human beard hair. These organs produce hair in response to androgens in the hamster. The flank organs of each hamster were depilated by applying a thioglycolate- based chemical depilatory (Surgex), and to one organ of each animal was applied 10-25 mg. of vehicle alone once a day, while to the other organ of each animal was applied an equal amount of vehicle containing inhibitor. After three weeks of such applications (five days a week), the flank organs were shaved and the amount of recovered hair (hair mass) from each was weighed. The extent of reduction in hair growth was expressed as the percent decrease in hair mass on the organ treated with inhibitor as compared to the organ treated with vehicle alone. As a control, one group of eight animals had both flank organs of each animal treated with vehicle alone. The results were as shown in Table 1 below.

Table 1

## Inhibition of Hair Growth by Sulfhydryl Reactive Compounds

Compound	Dose	Vehicle	Hair Mass		
			Treated (mg)	Untreated (mg)	Percent Reduction
Thioalicylic acid	20%	B	0.18 ± 0.04	1.64 ± 0.04	89 ± 2%
2-Mercaptoethylamine (Cysteamine)	20%	A	0.30 ± 0.09	1.89 ± 0.34	86 ± 3%
L-Cysteine methyl ester	20%	A	0.28 ± 0.07	1.91 ± 0.30	86 ± 3%
L-Cysteine ethyl ester	20%	A	0.49 ± 0.08	2.73 ± 0.15	82 ± 3%
N-Acetyl-L-Cysteine	15%	A	0.39 ± 0.07	2.13 ± 0.31	80 ± 4%
2,3,-Dimercapto-1-propanesulfonic acid	20%	A	0.64 ± 0.08	3.08 ± 0.27	79 ± 3%
Dimethylaminoethanethiol	20%	A	0.34 ± 0.05	1.77 ± 0.19	78 ± 6%
Phosphocysteamine	25%	E	0.50 ± 0.10	1.94 ± 0.17	74 ± 4%
3-Carboxypropyl disulfide	15%	A	0.70 ± 0.14	2.63 ± 0.26	74 ± 4%
3,3'-Thiodipropionic acid	20%	A	0.76 ± 0.12	2.80 ± 0.25	73 ± 4%
Diethyldithiocarbamic acid	15%	A	0.65 ± 0.09	2.28 ± 0.25	68 ± 7%
D-penicillamine	15%	A	0.57 ± 0.07	1.87 ± 0.3	65 ± 5%
Sulfasalazine	20%	C	0.88 ± 0.14	2.32 ± 0.21	61 ± 6%
D-Cysteine	10%	A	1.20 ± 0.17	2.92 ± 0.24	60 ± 3%
5'-Deoxy-5'-methylthioadenosine	10%	A	1.25 ± 0.17	2.97 ± 0.27	57 ± 6%
Captopril	10%	A	1.49 ± 0.20	3.50 ± 0.15	57 ± 5%
DL-α-Lipoic acid (reduced form)	15%	A	0.74 ± 0.09	1.73 ± 0.19	56 ± 6%
Cysteinyglycine	15%	A	0.93 ± 0.18	2.26 ± 0.26	55 ± 8%
D-penicillamine disulfide	15%	A	1.09 ± 0.23	2.36 ± 0.30	55 ± 4%
Isethionic acid	15%	A	1.45 ± 0.22	3.03 ± 0.31	50 ± 7%
meso-2,3,-Dimercaptosuccinic acid	20%	C	1.08 ± 0.16	2.23 ± 0.28	50 ± 5%
3,3'-Thiodipropionic acid dilauryl ester	20%	D	1.07 ± 0.10	2.15 ± 0.08	50 ± 4%
S-2-Aminoethyl-L-cysteine	20%	A	0.99 ± 0.20	2.15 ± 0.35	50 ± 11%
3,3'-Thiodipropionic acid dilauryl ester	5%	D	1.70 ± 0.21	2.39 ± 0.16	30 ± 7%

Table 1 (Continuation)  
Inhibition of Hair Growth by Sulfhydryl Reactive Compounds

Compound	Hair Mass				
	Dose	Vehicle	Treated (mg)	Untreated (mg)	Percent Reduction
3-(Methylthio)-propylamine Allyl sulfide DL- $\alpha$ -Lipoic acid (reduced form)	2%	A	0.97 $\pm$ 0.13	1.27 $\pm$ 0.10	22 $\pm$ 13%
	20%	B	1.74 $\pm$ 0.16	2.22 $\pm$ 0.22	17 $\pm$ 10%
	5%	B	2.67 $\pm$ 0.26	3.22 $\pm$ 0.32	16 $\pm$ 5%
Vehicles					
Vehicle A:	68% distilled H <sub>2</sub> O, 16% ethanol (100 proof), 5% propylene glycol, 5% dipropylene glycol, 4% benzyl alcohol, 2% propylene carbonate				
Vehicle B:	80% ethanol (190 proof), 17.5% distilled H <sub>2</sub> O, 2% propylene glycol dipelargonate (Emerest 2388), 0.5% propylene glycol				
Vehicle C:	Moisturizing lotion containing common cosmetic ingredients which include emulsifiers, detergents, and preservatives				
Vehicle D:	75% acetone, 20% propylene carbonate, 5% benzyl alcohol				
Vehicle E:	86% distilled H <sub>2</sub> O, 4% propylene glycol, 4% dipropylene glycol, 4% propylene carbonate, 2% ethanol				



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The preferred compositions are those that provided a reduction in hair growth of at least 30%, and more preferably at least 50%, when tested according to the above procedure.

5           The following biochemical properties of some of the sulfhydryl reactive compounds were tested: (1) the percent reduction in hair shaft cysteine caused by the compounds; (2) the ability of the compounds to form a cysteine-  
10 mixed disulfide in vitro; (3) the ability of the compound to form a cysteine-mixed disulfide in hair shafts; and (4) the ability of the compounds to reduce cystine.

15           The percent reduction in hair shaft cysteine caused by the sulfhydryl reactive compounds was measured according to the following procedure. Amino acid analysis of hamster flank organ hairs was carried out using a commercially available amino acid analysis  
20 system (Pico-Tag system, available from Waters Associates, Inc., Milford, MA). The hairs were thoroughly washed, then hydrolyzed by HCL vapors at 115°C. overnight. The hydrolyzed hairs (now free amino acids) were derivatized with  
25 phenylisothiocyanate to yield the phenylthiohydantion derivatives of the respective amino acids, which were then separated by C-18 reverse phase chromatography (HPLC), and quantitated by an in-line UV  
30 spectrophotometer. It is believed that the reduction of cysteine levels in hair shafts caused by some of the sulfhydryl active compounds is at least in part responsible for the reduction in hair growth caused by these  
35 compounds.

          The ability of the sulfhydryl reactive compounds to form cysteine-mixed disulfides in

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hair shafts was determined according to the following procedure. Groups of eight (8) Golden Syrian hamsters were treated topically with a sulfhydryl active compound on one flank organ (treated site) and the carrier vehicle without the sulfhydryl active compound on the other flank organ (control site). The carrier vehicles were the same as for the results achieved in Table 1. Following thirteen (13) treatments (Mon-Fri, over 18 days), hair shafts from the treated flank organs were harvested and analyzed for the presence of cysteine-mixed disulphides. It is believed that the ability of some of the sulfhydryl reactive compounds to form the cysteine-mixed disulfides in the hair shaft is at least in part responsible for the reduction in hair growth caused by these compounds, as the hair shaft proteins fail to undergo final post-translational maturation (disulfide formation).

The ability of the sulfhydryl reactive compounds to form cysteine-mixed disulfides in vitro was determined by incubating the sulfhydryl reactive compounds in test tubes, with either cystine or cysteine, under physiological conditions (i.e. pH 7.4 and at a temperature of 37°C.). The reaction of these compounds with cysteine or cystine was evaluated by HPLC analysis. It is believed that the ability of a sulfhydryl reactive compound to form a cysteine-mixed disulfide in vitro provides an indication that the compound is capable of forming cysteine-mixed disulfides with free cysteine present in hair follicle bulbs prior to cysteine incorporation into protein of the hair shaft when applied topically to the skin.

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The ability of sulfhydryl reactive compounds to reduce cystine was determined by incubating the respective sulfhydryl compound with cystine at physiological conditions of temperature and pH (37°C., pH 7.4). Following the incubation, the samples were derivatized and analyzed on HPLC as given above. For cysteamine, phosphocysteamine and dimethylcysteamine the samples were analyzed without derivatization, using an electrochemical detector instead of the UV detector used in amino acid analysis. The determination of cystine reduction by the compounds was based on generation of cysteine (free thiol) in the incubation mixture. It is believed that reducing the disulfide bond in cystine in hair proteins results in reduced hair growth.

The results of the testing of these properties are recorded in Table 2.

Table 2  
Biochemical Properties of Select Sulfhydryl Reactive Agents

<u>Sulfhydryl reactive agent</u>	<u>Percent reduction in hair shaft cysteine</u>	<u>Formation of Cysteine mixed disulfide in-vitro in hair shaft</u>	<u>Reduction of Cystine</u>
D-Penicillamine	50%	YES	ND*
Cysteamine	50%	YES	YES
Dimethyl cysteamine	28%	YES	YES
Phospho cysteamine	24%	YES*	ND*
Dimercaptopropanesulfonic acid	40%	YES	YES
Meso-dimercaptosuccinic acid	22%	NO	YES
Captopril	26%	YES	YES
5'-Deoxy methylthioadenosine	11%	NO	NO
Diethyl dithiocarbamic acid	18%	NO	NO
Thiosalicylic acid	14%	NO	NO
Sulfasalazine	(-2%)	NO	NO
Cysteinyglycine	ND*	ND*	YES
$\alpha$ -Lipoic acid	ND*	NO	NO

ND\*: Not Determined

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Other embodiments are within the  
claims.

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C L A I M S

1. . A process of reducing the rate of mammalian hair growth, comprising applying a non-depilatory composition including an effective amount of a sulfhydryl active compound to the skin, said compound reducing the rate of hair growth from said skin.
2. The process of claim 1, wherein after application said compound penetrates into the hair follicles in said skin and reacts with free cysteine in said hair follicle cells to form cysteine-mixed disulfides.
3. The process of claim 1, wherein said sulfhydryl active compound after application penetrates into the pre-ketanized hair shafts in said skin and reduce the disulfide bond in cystine in hair proteins.
4. The process of claim 3, wherein said sulfhydryl active compound also forms a mixed disulfide bond with one of the cysteine moieties in hair shaft proteins.
5. The process of claim 1, wherein said sulfhydryl active compound is cysteamine.
6. The process of claim 1, wherein said sulfhydryl active compound is D-penicillamine.
7. The process of claim 1, wherein said sulfhydryl active compound is dimethyl cysteamine.
8. The process of claim 1, wherein said sulfhydryl active compound is phosphocysteamine.
9. The process of claim 1, wherein said sulfhydryl active compound is captopril.
10. The process of claim 1, wherein said sulfhydryl active compound is meso-dimercaptosuccinic acid.

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11. The process of claim 1, wherein said  
sulfhydryl active compound is  
diethyldithiocarbamic acid.
12. The process of claim 1, wherein said  
5 sulfhydryl active compound is cysteinyl-glycine.
13. The process of claim 1, wherein said  
sulfhydryl active compound is D-cysteine.
14. The process of claim 1, wherein said  
sulfhydryl active compound is N-acetyl-cysteine.
- 10 15. The process of claim 1, wherein said  
sulfhydryl active compound is thiosalicylic  
acid.
16. The process of claim 1, wherein said  
sulfhydryl active compound is lipoic acid.
- 15 17. The process of claim 1, wherein said  
sulfhydryl active compound is 5'-deoxy-5'-  
methyl-thioadenosine.
18. The process of claim 1, wherein said  
sulfhydryl active compound is L-cysteine methyl  
20 ester.
19. The process of claim 1, wherein said  
sulfhydryl active compound is sulfasalazine.
20. The process of claim 1, wherein said  
sulfhydryl active compound is L-cysteine ethyl  
25 ester.
21. The process of claim 1, wherein said  
sulfhydryl active compound is 3-carboxypropyl  
disulfide.
22. The process of claim 1, wherein said  
30 sulfhydryl active compound is applied to the  
face.
23. The process of claim 1, wherein said  
sulfhydryl active compound has a free -SH group.
24. The process of claim 1, wherein said  
35 sulfhydryl active compound is a thiol without a  
free -SH group.

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25. The process of claim 1, wherein said sulfhydryl active compound is a thiol or disulfide that can be converted to a molecule with a free -SH group in cells.

5 26. The process of claim 1, wherein said composition reduces hair growth by at least 30% when tested according to the Golden Syrian Hamster protocol.

10 27. The process of claim 1, wherein said composition reduces hair growth by at least 50% when tested according to the Golden Syrian Hamster protocol.



## INTERNATIONAL SEARCH REPORT

International application No.  
PCT/US93/12266

## A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) :Please See Extra Sheet.

US CL :Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/46, 126, 150, 159, 423, 430, 440, 476, 550, 556, 562, 574, 665

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS, APS- SULFHYDRYL REACTIVE COMPOUNDS, BROADLY AND SPECIFICALLY, IN HAIR-TREATING COMPOSITIONS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 5,095,007 (AHLUWALIA) 10 MARCH 1992, SEE COLUMN 2, LINES 35-57 ESPECIALLY.	26-27
Y	US, A, 4,935,231 (PIGIET) 19 JUNE 1990, SEE ESPECIALLY COLUMNS 1-2 AND CLAIMS 7, 15 AND 16.	1-27
Y	WO, A, 91/10421 (TOURNIER ET AL.) 25 JULY 1991, SEE ESPECIALLY PAGES 1-2 AND CLAIMS 7,10 AND 12.	1-27

☐ Further documents are listed in the continuation of Box C.☐ See patent family annex.

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Date of the actual completion of the international search

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## A. CLASSIFICATION OF SUBJECT MATTER:

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## A. CLASSIFICATION OF SUBJECT MATTER:

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